Eradication of infectious diseases—past and future

S159 Eradication of infectious diseases—past and future

W. Dowdle. *Task Force for Child Survival and Development, Decatur, GA, USA*

Eradication has been variously defined, but, in essence, is the absence of a disease agent in nature as the result of deliberate control efforts. Intervention efforts are no longer needed. Smallpox is the only infectious disease that has been eradicated. Immunization against smallpox is no longer practiced. Programs are underway to eradicate poliovirus and Guinea worm. Previous eradication programs targeting malaria, yellow fever and yaw failed to achieve their goals, but led to better understanding of the biological, social, political and economic complexities of disease eradication. Distinct biological features and operational factors define eradicability. Three criteria are of primary importance: (1) effective intervention is available to interrupt transmission of the agent; (2) practical, sensitive and specific diagnostic tools are available to detect infection that can lead to transmission; and (3) humans are essential for the agent life cycle. Eradication is the ultimate goal of every effective public-health program, whether stated or not. Fundamental issues relate to specific versus comprehensive goals and time-limited versus long-term goals. Biological plausibility is but one of the factors to consider. Deciding on the appropriate eradication goal also requires careful evaluation of cost-effectiveness, resource availability, and political will. All of these issues are now under discussion for several proposed potential candidates for eradication: measles, rubella, onchocerciasis, and lymphatic filariasis. A time-limited eradication goal is a major commitment and an awesome responsibility, with no room for failure. Eradication programs work best where health system infrastructures are strong. Where infrastructures are weak, eradication programs can be powerful building tools.

S160 Measles and poliomyelitis eradication: the protagonists for global eradication

C. de Quadros. *Pan American Health Org., Program Vaccines and Immunizat., Washington, D.C., USA*

In September 1985, PAHO targeted poliomyelitis to be eradicated from the Americas by 1990. The strategy for poliomyelitis eradication included routine vaccination with oral poliomyelitis vaccine (OPV), complemented by national immunization days (NIDs) with OPV, aimed at rapidly interrupting chains of transmission. The NIDs, and surveillance for detection of cases of acute flaccid paralysis (AFP) with laboratory investigation for the presence of wild poliovirus in their stools, proved to be two key components of eradication. The third key component of the strategy was the implementation of special 'mop-up' operations of house-to-house OPV vaccination in those few municipalities where poliomyelitis was still prevalent. The Americas were certified polio-free in September 1994 and by July 1996. Over 7 years have elapsed since the last confirmed case of paralytic poliomyelitis due to wild poliovirus was detected on 23 August 1991, in Peru. This fact is of historical significance in the annals of public health, and the strategies developed by PAHO are now being implemented worldwide for the achievement of polio eradication by the year 2000. During 1998 there were less than 5000 cases reported worldwide, the lowest number ever reported, and the target of global eradication by the year 2000 is well in our grasp. With poliomyelitis eradicated from the Americas, countries set the target of eradication of measles from the Western Hemisphere by the year 2000. Strategies recommended by PAHO to achieve this goal include national immunization campaigns conducted in a short period of time, usually 1 month, aimed at immunizing all children between 1 year and 15 years of age with measles vaccine regardless of previous vaccination status, and maintenance of high immunization levels in the new cohorts of newborns. These campaigns, aiming at interrupting all chains of transmission, are followed by intense surveillance of suspected measles cases, prompt investigation and outbreak prevention whenever a confirmed case of measles occurs. As a result of implementation of this strategy, only 2109 confirmed measles cases were reported in 1996, the lowest number of total measles cases since measles surveillance began in the Americas. In the English-speaking Caribbean, it has now been over 6 years since the last laboratory-confirmed case. No cases of measles have been reported for the past 4 years in Cuba and Chile, and present surveillance systems are unable to detect measles cases in most countries of the region. An obstacle to measles eradication is the accumulation of susceptible children which occurs among 1–5-year-olds because the vaccine is not 100% efficacious and coverage never reaches 100%. To prevent this accumulation of susceptibles and prevent outbreaks, PAHO recommends that countries undertake 'follow-up' vaccination campaigns targeting all children 1–5 years of age, regardless of previous vaccination status, every 4–5 years. The absence of 'follow-up' campaigns in some few countries or areas in the Americas resulted in an outbreak of measles in Brazil in 1997, following a possible importation from Europe, and in Argentina in 1998, following an importation from the outbreak in Brazil. In total, over 50 000 cases occurred in the Americas in 1997, over 95% in Brazil, and nearly 10 000 in 1998, over 85% in Argentina. By now, these outbreaks are under control and the target of eradication by the year 2000 is expected to be achieved. As was the case with smallpox, the examples of polio and measles demonstrate that humankind can conquer other diseases. However, much remains to be done, and there is therefore a need for continuous political commitment, which should be translated into allocation of resources. Participation and collaboration of all sectors of society in every country will be fundamental for the achievement of these objectives. The success of measles eradication in the Americas will set the stage for the global eradication of this disease in the first decade of the 21st century.

S161 Can malaria be globally eradicated?

C.G. Meyer. *Institut für Tropenmedizin, Berlin, Germany*

Malaria is a major global health problem and *Plasmodium falciparum* malaria remains a leading cause of mortality in many tropical countries. Nearly half of the world's population is under continuous threat from malaria, with an estimated 400–500 million clinical cases and more than 2 million deaths occurring every year. The situation is complicated by the emergence and spread of resistance to many antimalarial drugs. In addition to good treatment facilities in areas of high transmission, chemoprophylaxis in pregnancy, use of insecticide-treated bednets and household spraying, vaccination is primarily considered to supplement current strategies of disease prevention and control.

After the availability of *Plasmodium falciparum* cultivation and the analysis of parasite antigens with successful protection of mice and monkeys following immunization with distinct antigens, several human vaccination trials have failed so far to provide sufficient protective immunity. Other approaches are now under study, with some 20 candidate molecules and DNA vaccines being tested. Target antigens are pre-erythrocyte and erythrocyte stages, gametes, and pathogenic parasitic metabolites. A major obstacle is the complexity

of the antigenic structure of the parasite, with large numbers of different epitopes that are, in part, stage-specific and, furthermore, may vary between strains. Adjuvants also influence the type of immune response. The growing knowledge of pathogenesis, and host-dependent genetic and immunologic factors involved in the clinical outcome of *P. falciparum* malaria, and the insight into the parasite's evasion mechanisms, help us to understand the interactions of this infectious agent with the host's immune system. We now believe that malaria vaccines will eventually be available. We do not, however, believe that vaccines alone will lead to the eradication of this disease.

S162 The future of global strategies for vaccination: WHO perspectives

P.-H. Lambert. *WHO, Vaccine Research & Devel. Unit, Geneva, Switzerland*

Future vaccination strategies will certainly be related to the potential impact of vaccination on morbidity and mortality directly or indirectly associated with specific infectious diseases. About 1.8 million children die of infection in the neonatal period (0–4 weeks of age), particularly in Asia and Africa. The main causes of death are bacterial infections caused by *Staphylococcus aureus*, group A streptococci, *Streptococcus pneumoniae*, Gram-negative coliforms and *Salmonella* as well as neonatal tetanus. During the post-neonatal period (1–12 months), severe infant infections are responsible for over 2 million deaths. In the developing world, the major causes are acute respiratory infections due to pneumococci, *Haemophilus influenzae* or pertussis as well as diarrhea caused by rotavirus, shigella, *Salmonella* or *E. coli*. This contrasts with the greater importance of respiratory viruses (RSV, parainfluenza and influenza), urinary infections, and rotavirus diarrhea in industrialized countries. Although a number of new vaccines are now becoming available to meet this challenge, vaccination strategies to prevent early-life infectious diseases should be selected and adapted accordingly. They will include maternal immunization for early neonatal infections, as well as vaccination in early infancy (0–3 months) for early-occurring diseases. Problems to be solved are mainly related (1) to safety issues (maternal or neonatal immunization), (2) to immunologic immaturity and T-cell polarization (0–3 months immunization), (3) to the duration of induced protection and memory, and (4) to inhibition of infant responses by maternal antibodies.

Recent developments in cardiovascular infections

S163 Do we still need prophylaxis against infective endocarditis?

E. Gutschik. *Department of Clinical Microbiology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark*

The answer is yes, even according to a recent population-based, case-control study from Philadelphia, USA (Ann Intern Med 1998;129: 761–9) challenging the current recommendations for prophylaxis for infective endocarditis (IE). The findings indicate that dental treatment is not a risk factor. However, differences in dental health, dental status and dental care between case patients and controls were not considered. This study will not change our attitude towards the necessity for antimicrobial prophylaxis, but underlines the need for data regarding the correlation between the magnitude of bacteremia (CFU/mL blood) in connection with dental procedures and the incidence of IE. It is likely that prophylaxis should be downgraded to 'not recommended' for some dental procedures. Since oral microorganisms are still responsible for most cases of IE, it is obvious that prevention should be upgraded, with maintenance of better dental care in patients at risk for IE. Prophylaxis in children, especially with major congenital heart conditions, requires further investigation and discussions. Prevention of nosocomial endocarditis represents a formidable clinical challenge, with the introduction of new cardiac devices like implantable cardiovascular defibrillators and left ventricular assist devices, raising questions of hardware removal in cases of infection or chronic suppressive antimicrobial therapy. The incidence and mortality of prosthetic valve endocarditis are still unacceptably high. Here also we should focus on prevention (surgical techniques, surgical materials, treatment of perioperative bacteremias, dental health) rather than efforts to amplify antimicrobial prophylaxis.

S164 New antibiotic treatment modalities

J.M. Entenza, J. Vouillamoz, M.P. Glauser, P. Moreillon. *Infectious Diseases, CHUV, Lausanne, Switzerland*

Treatment of *Staphylococcus aureus* and streptococcal endocarditis requires prolonged administration of parenteral β-lactams or vancomycin. Newer quinolones are active against Gram-positive bacteria, are well absorbed after oral administration, and have a prolonged serum $t1/2$, allowing once-daily dosage. Levofloxacin, trovafloxacin and moxifloxacin were tested in rats with *S. aureus* or streptococcal experimental endocarditis (EE). They were compared to ciprofloxacin (Cipro) and vancomycin (Vanco) for *S. aureus*, or ceftriaxone for streptococci. The risk of resistance selection was examined. Against Cipro-susceptible *S. aureus*, all three new quinolones were equivalent or more active than Cipro and Vanco in vitro and in vivo, and were markedly less prone than Cipro to select for quinolone resistance. However, they were ineffective against *S. aureus* already resistant to Cipro. Two experimental quinolones (Y-688 and S-34109) with high in vitro activity against Cipro-resistant *S. aureus* also failed in rats, and selected for mutants with increased MICs. Thus, once resistant to Cipro, *S. aureus* may easily acquire additional mutations, making it resistant to the most powerful quinolones. Against streptococci, levofloxacin was effective against EE due to penicillin-susceptible and -resistant isolates. In contrast, trovafloxacin failed in similar experiments. Time-kill experiments indicated that very low concentrations (×2 and ×4 MIC) of levofloxacin were more bactericidal than trovafloxacin against streptococci, suggesting that higher doses of this drug should be used in this situation. This was not observed for *S. aureus*. We conclude that newer quinolones might be convenient and effective against Cipro-susceptible (but not -resistant) *S. aureus* and streptococcal infections. Moreover, they are less prone than older quinolones to select for resistance.

S165 Anti-infective impregnation of vascular prostheses and cardiac prosthetic valves: rationale and experimental evidence

J. Steckelberg, *Mayo Clinic, Infectious Diseases and Internal Medicine, Rochester, MN, USA*

Anti-infective agents have been bound to a variety of implantable or indwelling medical devices in an attempt to increase local concentrations of antimicrobial or antiseptic agents and to reduce the risk of foreign body infections. This approach has been shown to be successful in some clinical settings (such as silver-coated intravascular catheters) but unsuccessful in others. For the prevention or treatment